

## **EXHIBIT 1, Tab 6**



**S I G N**

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Network**

# **Management of Early Rheumatoid Arthritis**

**A National Clinical Guideline**

**December 2000**

**KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS**

## STATEMENTS OF EVIDENCE

1 <sup>++</sup>	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 <sup>+</sup>	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 <sup>-</sup>	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2 <sup>++</sup>	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2 <sup>+</sup>	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 <sup>-</sup>	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

## GRADES OF RECOMMENDATIONS

<b>A</b>	At least one meta-analysis, systematic review, or RCT rated as 1 <sup>++</sup> , and directly applicable to the target population; <i>or</i> A body of evidence consisting principally of studies rated as 1 <sup>+</sup> , directly applicable to the target population, and demonstrating overall consistency of results
<b>B</b>	A body of evidence including studies rated as 2 <sup>++</sup> , directly applicable to the target population, and demonstrating overall consistency of results; <i>or</i> Extrapolated evidence from studies rated as 1 <sup>++</sup> or 1 <sup>+</sup>
<b>C</b>	A body of evidence including studies rated as 2 <sup>+</sup> , directly applicable to the target population and demonstrating overall consistency of results; <i>or</i> Extrapolated evidence from studies rated as 2 <sup>++</sup>
<b>D</b>	Evidence level 3 or 4; <i>or</i> Extrapolated evidence from studies rated as 2 <sup>+</sup>

## GOOD PRACTICE POINTS

- ☒ Recommended best practice based on the clinical experience of the guideline development group

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## GUIDELINE DEVELOPMENT GROUP

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## Notes for users of the guideline

### DEVELOPMENT OF LOCAL GUIDELINES

It is intended that this guideline will be adopted after local discussion involving clinical staff and management. The Area Clinical Effectiveness Committee should be fully involved. Local arrangements may then be made for the derivation of specific local guidelines to implement the national guideline in individual hospitals, units and practices and for securing compliance with them. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

SIGN consents to the copying of this guideline for the purpose of producing local guidelines for use in Scotland.

### STATEMENT OF INTENT

This report is not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve.

These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor in light of the clinical data presented by the patient and the diagnostic and treatment options available.

Significant departures from the national guideline as expressed in the local guideline should be fully documented and the reasons for the differences explained. Significant departures from the local guideline should be fully documented in the patient's case notes at the time the relevant decision is taken.

A background paper on the legal implications of guidelines is available from the SIGN executive.

### REVIEW OF THE GUIDELINE

This guideline was issued in December 2000 and will be reviewed in 2002 or sooner if new evidence becomes available. Any amendments to the guideline in the interim period will be noted on the SIGN website. Comments are invited to assist the review process. All correspondence and requests for further information regarding the guideline should be addressed to:

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## Abbreviations

<b>ACR</b>	American College of Rheumatology
<b>ANA</b>	Antinuclear antibody
<b>ARA</b>	American Rheumatism Association
<b>ARAMIS</b>	Arthritis, Rheumatism and Aging Medical Information System
<b>BMI</b>	Body mass index
<b>Cox</b>	Cyclooxygenase
<b>CRP</b>	C-reactive protein
<b>CT</b>	Connective tissue
<b>DAS</b>	Disease activity score
<b>DMARD</b>	Disease modifying anti-rheumatic drug
<b>EBV</b>	Epstein-Barr virus
<b>ESR</b>	Erythrocyte sedimentation rate
<b>EULAR</b>	European League against Rheumatism
<b>FBC</b>	Full blood count
<b>GI</b>	Gastrointestinal
<b>GP</b>	General Practitioner
<b>HAQ</b>	Health assessment questionnaire
<b>HLA</b>	Human leukocyte antigen
<b>HRT</b>	Hormone replacement therapy
<b>IBD</b>	Inflammatory bowel disorder
<b>IM</b>	Intramuscular
<b>LFT</b>	Liver function test
<b>MCP</b>	Metacarpophalangeal
<b>MTP</b>	Metatarsophalangeal
<b>NNT</b>	Number needed to treat
<b>NSAID</b>	Nonsteroidal anti-inflammatory drug
<b>OT</b>	Occupational therapy
<b>PIP</b>	Proximal interphalangeal
<b>RA</b>	Rheumatoid arthritis
<b>RCT</b>	Randomised controlled trial
<b>RF</b>	Rheumatoid factor
<b>SC</b>	Subcutaneous
<b>SIGN</b>	Scottish Intercollegiate Guidelines Network
<b>SLE</b>	Systemic lupus erythematosus
<b>SSRI</b>	Selective serotonin re-uptake inhibitor
<b>TENS</b>	Transcutaneous electrical nerve stimulation
<b>TNF</b>	Tumour necrosis factor
<b>U&amp;E</b>	Urea & electrolytes

## Summary of recommendations

### TREATMENT OVERVIEW

**RA should be treated as early as possible with disease modifying anti-rheumatic drugs (DMARDs) to control symptoms and delay disease progression.**

- ☑ ▪ All patients with persistent inflammatory joint disease (> 6-8 weeks duration) already receiving simple analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) should be considered for referral for specialist rheumatology opinion and DMARD therapy, preferably within 12 weeks.
- ☑ ▪ Patient education should be undertaken by all members of the multidisciplinary teams in both primary and secondary care.
- Patients should be provided with an information leaflet/booklet, and if possible, one-to-one education.

### NSAIDs

**The lowest NSAID dose compatible with symptom relief should be prescribed.**

**NSAIDs should be reduced and if possible withdrawn when a good response to DMARDs is achieved.**

- ☑ ▪ Simple analgesics should be used in place of NSAIDs if possible and DMARDs should be introduced early to suppress disease activity.
- Only one NSAID should be prescribed at a time.
- Prescribers should be aware of the many potential drug interactions with NSAIDs and the side effect profiles of different drugs.
- NSAIDs should be avoided in patients taking anticoagulants or corticosteroids.

**Introduce gastroprotection in RA patients > 65 years and in those with a past history of peptic ulcer.**

### DMARDs

**Early DMARD therapy in RA is important to maintain function and reduce later disability.**

**DMARD therapy should be sustained in inflammatory disease in order to maintain disease suppression.**

- ☑ DMARD choice should take into account patient preference and existing co-morbidity.

**Sulphasalazine, methotrexate, IM gold, and pencillamine are equally effective DMARDs.**

**Sulphasalazine and methotrexate are the current DMARDs of choice due to their more favourable efficacy/toxicity profiles.**

- ☑ ▪ Patients should be counselled about the benefits and risks of specific DMARDs, and should be provided with additional written information.
- Good liaison between primary and secondary care is essential. Rheumatology nurse specialists have an important role in this aspect of care.
- Monitor for continued efficacy (ESR/CRP, number of tender and swollen joints, duration of morning stiffness, function).

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- ☑ ▪ Monitor toxicity using British Society of Rheumatology/local guidelines or manufacturers' data sheet recommendations.
- Clear advice about the monitoring of specific DMARDs should be available to the patient, GP and practice nurse.

**B** At present the balance of evidence does not support the routine use of combination DMARD therapy in early RA.

## INTRA-ARTICULAR CORTICOSTEROIDS

- ☑ ▪ Intra-articular injections can be used for rapid, and sometimes sustained, symptomatic relief in 'target' joints.
- Intra-articular injections to any one joint should not be given more than three times in one year.
- When administering intra-articular injections:
  - use sterile technique
  - advise patients how to seek help if joint fails to settle after injection
  - always consider possible septic arthritis in differential diagnosis of mono/oligo flare in RA.

## CORTICOSTEROID THERAPY

**B** Oral corticosteroids are not recommended for routine use, as there is no sustained clinical or functional benefit and there is a high risk of toxicity with long term use.

- ☑ ▪ Inform patients of the risks of corticosteroids prior to prescription and issue a steroid warning card.
- Intramuscular corticosteroid allows control of dose and duration of therapy and may be preferable to oral therapy.
- Oral corticosteroids should be withdrawn slowly to avoid rebound flare of symptoms.

**D** The lowest possible dose of corticosteroid should be used for the shortest possible time.

Monitor patients closely for adverse corticosteroid effects. Be alert to the possibility of diabetes, cataract and infection. Inform patients not previously infected of the danger of chicken pox/shingles exposure.

- ☑ Ensure adequate prophylaxis and treatment of osteoporosis in patients taking oral corticosteroids.

## THE ROLE OF THE MULTIDISCIPLINARY TEAM

- ☑ All patients with early RA should have access to a range of health professionals, including general practitioner, rheumatologist, nurse specialist, physiotherapist, occupational therapist, dietitian, podiatrist, pharmacist and social worker.

**C** Skilled occupational therapy advice should be available to those experiencing limitations in function.

Resting and working splints can be used to provide pain relief.

**B** Patients should be encouraged to undertake simple dynamic exercises.

- ☑ Podiatry referral should be offered to all patients.

# 1 Introduction

## 1.1 BACKGROUND

Rheumatoid arthritis (RA) affects approximately 1% of the population and is more common in women than in men. The course of RA is variable and unpredictable but for a significant number of patients it is a severe disease resulting in persistent pain and stiffness, progressive joint destruction, functional decline and premature mortality.<sup>1-3</sup> Equally important to affected individuals is the potential loss of social and financial independence.<sup>4</sup>

The disease also exerts a considerable burden on society in terms of direct (e.g. medical care) and indirect costs (e.g. effects on the individual's ability to work, see *section 3.6*).<sup>5, 6</sup>

## 1.2 THE NEED FOR A GUIDELINE

The traditional management of RA, the 'treatment pyramid', begins with mild, mainly symptomatic measures and defers the use of disease modifying drugs until the disease has progressed further. However, increasing recognition that, for many patients, RA is not a benign condition with a good prognosis has prompted a re-evaluation of therapeutic strategies and the clinical effectiveness of the traditional approach has been widely challenged.<sup>7-9</sup> It has been shown that erosive change, leading to joint destruction, often occurs in early disease<sup>10-14</sup> and that early loss of function may be irreversible. In addition, evidence is now accumulating that early more aggressive intervention can improve longer term disease outcome.<sup>15</sup> There is therefore a need for an evidence-based guideline for the management of early RA.

## 1.3 REMIT

This guideline addresses diagnosis of early RA, its pharmacological treatment, and the role of the multidisciplinary team in improving care of the RA patient. It is hoped that the guideline will inform standards for practice for rheumatologists, general practitioners (GPs), rheumatology nurse specialists, physiotherapists, occupational therapists, dietitians, podiatrists and pharmacists.

At present there is no formal definition of 'early RA'. It is defined in this guideline as disease duration of < 5 years from onset of symptoms.

The guideline does not cover:

- Treatment of co-morbidity (e.g. anaemia, osteoporosis)
- Complications of drug therapy and their management
- Treatment of extra-articular disease (e.g. vasculitis, ocular complications, amyloid)
- Surgical intervention
- Management of children with arthritis.

## 1.4 GRADING OF RECOMMENDATIONS

This guideline introduces for the first time a revised system for grading guideline recommendations. A key to the new grading system is provided on the inside front cover. Further information is available on the SIGN website: [www.sign.ac.uk](http://www.sign.ac.uk).

## 2 Diagnosis of early rheumatoid arthritis

Early diagnosis of RA is a prerequisite for early treatment and is not always easy to achieve. Diagnosis relies heavily on history taking and clinical examination and less on investigations.

The American College of Rheumatology (ACR; previously the American Rheumatism Association) criteria for the classification of RA<sup>16</sup> illustrates this (see *Annex 2*). The ACR criteria are, however, primarily a research tool and are much less useful in routine clinical practice.

### 2.1 CLINICAL FEATURES

A typical patient with early RA will describe pain, stiffness and swelling in the joints that is worse in the morning and after inactivity. Examination (see *Table 1*) reveals symmetrical swelling and tenderness of the small joints of the hands and feet (and to a variable extent the larger joints) and the presence of synovitis (i.e. soft tissue swelling in relation to the joint). Systemic 'flu-like' symptoms are not uncommon. Atypical presentations of RA include patients with mainly girdle joint involvement mimicking polymyalgia rheumatica and those with persistent monoarthritis.

These findings are not, however, exclusive to RA and may occur in a number of other inflammatory arthropathies. In early disease, therefore, differential diagnosis should always be considered (see *Table 2*).

### 2.2 INVESTIGATION

There is no single diagnostic test for RA. Investigations are used largely to support the clinical diagnosis and negative results do not exclude the diagnosis of RA. Investigations which may be helpful in making the diagnosis of early RA are shown in *Table 3*.

*Table 1*

#### ASSESSING A PATIENT PRESENTING WITH INFLAMMATORY ARTHRITIS

##### Essential aspects of the consultation

###### History

- pain
- stiffness after inactivity
- joint swelling
- fatigue

###### Examination

- affected joints
- synovitis vs. bony swelling/deformity
- range of movement
- extra-articular features

##### Desirable aspects of the consultation

Functional status, e.g. health assessment questionnaire (HAQ)<sup>17</sup>

Impact of disease

Social circumstances/depression/anxiety

## 2 DIAGNOSIS OF EARLY RHEUMATOID ARTHRITIS

Table 2

## DIFFERENTIAL DIAGNOSIS OF EARLY RA

- 
- Viral arthritis (e.g. parvovirus, rubella)
  - Reactive arthritis (e.g. post-infective: throat, gut, sexually acquired)
  - Seronegative spondyloarthropathy (e.g. psoriatic, ankylosing spondylitis, inflammatory bowel disease)
  - Connective tissue disease (e.g. systemic lupus erythematosus (SLE), scleroderma)
  - Polymyalgia rheumatica
  - Polyarticular gout
  - Fibromyalgia
  - Medical conditions presenting with arthropathy (e.g. sarcoidosis, thyroid disease, infective endocarditis, haemochromatosis, diabetic cheiroarthropathy, paraneoplastic syndromes, multiple myeloma).
- 

Table 3

## INVESTIGATIONS HELPFUL IN DIAGNOSIS OF RA

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Investigation	Findings
<b>Erythrocyte sedimentation rate (ESR)/ C-reactive protein (CRP) / plasma viscosity</b>	Usually elevated in RA but may be normal
<b>Full blood count (FBC)</b>	Normochromic, normocytic anaemia and reactive thrombocytosis common in active disease
<b>Urea &amp; electrolytes (U&amp;E), Liver function tests (LFT)</b>	Mild elevation of alkaline phosphatase and gamma-GT common in active disease
<b>Uric acid/ synovial fluid analysis</b>	Will assist in excluding polyarticular gout
<b>Urinalysis</b>	Microscopic haematuria/proteinuria may suggest connective tissue disease
<b>Rheumatoid factor (RF)</b>	RF positive in only 60-70% RA patients. May be positive in other inflammatory diseases and normal individuals
<b>Antinuclear antibody (ANA)</b>	Positive in SLE and related conditions. ANA positive in up to 30% of RF-positive RA patients. May be weakly positive in up to 10% of normal individuals
<b>Radiology</b>	May be normal or may show periarticular osteopenia and/or erosions

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## MANAGEMENT OF EARLY RHEUMATOID ARTHRITIS

**2.3 PROGNOSTIC FEATURES IN EARLY RA**

Predicting outcome in RA in individual patients at disease outset is difficult. Improved understanding of prognostic features would help to identify patients with serious disease who require aggressive therapy and protect those with mild disease from exposure to potentially toxic treatment. Indicators of poor outcome (radiological, functional, mortality) are:

- many active joints<sup>18–20</sup>
- high ESR or CRP at outset<sup>12, 21–23</sup>
- positive rheumatoid factor<sup>19, 24–26</sup>
- early radiological erosions<sup>27</sup>
- poorer scores of function (e.g. HAQ) at outset<sup>18,19, 28, 29</sup>
- adverse socio-economic circumstances and lower educational level<sup>30–34</sup>



### 3 Principles of treatment

#### 3.1 EARLY INITIATION OF TREATMENT

It is well documented that the function of patients with RA will decline over time.<sup>35-37</sup> The goals of treatment, therefore, are symptom control, reduction of joint damage and disability and maintenance or improvement of quality of life. Whilst current therapies seldom achieve remission, they can slow disease progression and thereby reduce functional loss.

*Evidence level 2<sup>+</sup>*



**RA should be treated as early as possible with disease modifying anti-rheumatic drugs (DMARDs) to control symptoms and delay disease progression.**

- ☑ All patients with persistent inflammatory joint disease (>6-8 weeks duration) already receiving simple analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) should be considered for referral for specialist rheumatology opinion and DMARD therapy, preferably within 12 weeks.

#### 3.2 MULTIDISCIPLINARY TEAM APPROACH

Effective high quality treatment of early RA is multifaceted and involves the GP, rheumatologist, physiotherapist, occupational therapist, nurse specialist, dietitian, podiatrist, pharmacist and social worker.<sup>38</sup> A shared care approach between primary and secondary care physicians,<sup>39</sup> facilitated by practice nurses and rheumatology nurse specialists, ensures optimum monitoring of the efficacy and toxicity of drug therapy and the prompt identification of the complications of RA and its treatments.

#### 3.3 PATIENT EDUCATION

A common approach to patient education should be adopted by all members of the multidisciplinary team to ensure that patients receive a consistent health message (see Annexes 9, 10 and 11).<sup>40</sup> Patient education leaflets increase knowledge about the disease.<sup>41</sup> Educational interventions including a psychobehavioural component in addition to providing information appear to have better outcomes in terms of pain relief, joint protection and functional disability, but are labour intensive.<sup>42, 43</sup>

Patient led self-management education programmes (see Annex 11 for useful contacts) are increasing in popularity but evidence of their effectiveness is still limited.<sup>44, 45</sup> Careful evaluation of these programmes would be required in Scotland if they are to be made available more widely.

- ☑ Patient education should be undertaken by all members of the multidisciplinary teams in both primary and secondary care.
- ☑ Patients should be provided with an information leaflet/booklet, and if possible, one-to-one education.

#### 3.4 ASSESSMENT OF RESPONSE TO TREATMENT

Quantification of disease activity and outcome is important in assessing, comparing and standardising treatment of RA. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have both devised disease activity

## MANAGEMENT OF EARLY RHEUMATOID ARTHRITIS

scores which use composite measures so that comparisons can be made between different studies. Both scoring systems are detailed in Annex 5.

**Clinical measures of response to treatment include:**

- patient opinion (global assessment; see Annex 5)
- physician opinion (global assessment)
- extent of synovitis (number of swollen or tender and both swollen and tender joints)
- duration/severity of stiffness after inactivity
- functional ability (e.g. HAQ score; see Annex 4).

**Laboratory measures of response to treatment include:**

- acute phase response (ESR, CRP)
- anaemia
- radiological progression.

### 3.5 HOSPITAL ADMISSION

Selected patients may benefit from more intensive hospital-based treatment from the multidisciplinary team. Most studies comparing inpatient therapy with intensive outpatient therapy have demonstrated the superiority of the former.<sup>38, 46, 47</sup> One study has compared inpatient with day patient multidisciplinary therapy for patients with uncomplicated active RA and has shown these approaches to be clinically equivalent with little difference in economic costs.<sup>48</sup> However, a proportion of the costs of day patient treatment are borne by the patient and practical limitations such as travelling time and social circumstances make this option unsuitable for some patients. Thus it is essential that specialist inpatient facilities are maintained for selected RA patients.

### 3.6 COST OF UNTREATED DISEASE

The costs incurred in delayed treatment of RA are considerable. These include:

- Personal costs
  - lost work opportunities
  - decreased leisure activities
  - stress on relationships
- Costs to society
  - loss of working skills of RA individuals
  - loss of contributions to the home
  - the burden of economic cost for care.

Work disability can occur early in the course of RA, especially in those with manual occupations.<sup>5, 36</sup> Early intervention through retraining and liaison with the patient's employer will help to keep the patient in work for as long as practical and minimise the economic impact of the disease. The most important predictors of work disability are poorer function at the outset, a poorer education level and older age.<sup>3</sup> Many patients stop work in the first year after RA onset, highlighting the need for early and effective intervention if work disability is to be avoided.

Overall, patients in the worst functional quartile experience 2.6 times the personal financial cost of those in the best quartile. The hospital costs of the worst quartile are 6.8 times as high. Patients with poor and declining function from the start experience much higher costs of care overall.<sup>49, 50</sup>

Evidence level 2<sup>+</sup>

## 4 Pharmacological management

### 4.1 ANALGESICS

Analgesics in early RA are used as an adjunct to NSAID and DMARD therapy. There is evidence that paracetamol, coproxamol, nefopam, and codeine are effective in reducing pain in RA.<sup>51-55</sup> Most of these trials were carried out more than 20 years ago and can be criticised for small patient numbers and short duration. Only a very small proportion of rheumatoid patients is likely to be controlled with analgesics alone.

- ☑ Simple analgesics should be used in place of NSAIDs if possible and DMARDs should be introduced early to suppress disease activity.

### 4.2 NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

There is abundant evidence that NSAIDs are effective and provide symptomatic relief of pain and stiffness without influencing the progression of disease.<sup>56, 57</sup> The choice of short-, medium- or long-acting preparations can be tailored to fit a patient's particular lifestyle.

NSAIDs act by inhibiting cyclooxygenase (Cox) pathways. There are considered to be two isoforms of Cox. Cox1 produces prostaglandins which are cytoprotective and regulatory (GI mucosa, platelets and renal endothelium). Cox2 produces prostaglandins which mediate pain and inflammation and are the preferred targets in RA (see section 4.2.4).

- ☑ Prescribers should be aware of the many potential drug interactions with NSAIDs and the side effect profiles of different drugs (see Annex 6 and the *British National Formulary*).<sup>58</sup>

#### 4.2.1 ADVERSE EFFECTS OF NSAIDs

Toxicity is a major limiting factor and side effects are related to dose and duration of therapy.<sup>59, 60</sup> Common side effects (especially in the elderly) are gastrointestinal toxicity, fluid retention and hypertension. Other less common but potentially serious side effects are renal disease and hypersensitivity (including asthma). Uncommon and not usually serious side effects are headaches, dizziness, tinnitus, rash (particularly with fenbufen) and abnormal LFTs (particularly with diclofenac).

Evidence level 1<sup>+</sup>

#### 4.2.2 GASTROINTESTINAL TOXICITY

The use of NSAIDs is associated with gastrointestinal (GI) toxicity.<sup>59, 60</sup> The following side effects occur to a varying extent with all preparations and all routes of administration:

- dyspepsia
- gastric erosions
- peptic ulceration
- small bowel inflammation and bleeding<sup>61</sup>
- perforation
- haematemesis or melaena
- occult GI blood loss and anaemia

## MANAGEMENT OF EARLY RHEUMATOID ARTHRITIS

According to the Arthritis, Rheumatism and Aging Medical Information System (ARAMIS), 13 of every 1000 RA patients who take NSAIDs for one year have a serious gastrointestinal complication. The annual relative risk of mortality attributed to NSAID-related GI adverse effects is four times that for those not using NSAIDs.<sup>59</sup>

The rate of NSAID-related serious GI complications requiring hospitalisation has decreased in recent years. The reason for this is likely to be multifactorial. Intensive education programmes have alerted physicians and patients to the use of newer, less toxic NSAIDs and non-NSAID analgesics in populations at high risk. There has also been a much wider use of gastro-protective therapy.

Risk factors for NSAID-associated gastroduodenal ulcers are listed in Table 4.

Table 4

## RISK FACTORS FOR NSAID ASSOCIATED GASTRODUODENAL ULCERS

Definite risk factors	Possible lifestyle factors
Advanced age ( <i>linear increase in risk</i> )	Cigarette smoking
History of ulcer	Alcohol consumption
Higher doses of NSAIDs	
Combination use of NSAIDs	
Concomitant use of corticosteroids	
Co-morbidity	

Note: Concomitant administration of anticoagulants will increase the risk of GI haemorrhage.

Some patients who have serious GI complications do not report antecedent dyspepsia. Thus every possible strategy should be employed to minimise risks of GI-related toxicity,<sup>59</sup> e.g. smoking cessation, and alcohol reduction. Eradication of *Helicobacter pylori* in NSAID-associated peptic ulcers has not been shown to be of value (see the *SIGN Guideline on Helicobacter pylori: eradication in dyspeptic disease, which is currently under review*).<sup>62</sup>

Surveillance and endoscopic studies have confirmed that the incidence of GI mucosal injury is reduced with nabumetone, etodolac and meloxicam. Mefenamic acid, azapropazone and piroxicam are considered unacceptably toxic for long-term use in RA.<sup>63, 64</sup>

If NSAID use is unavoidable, gastroprotective agents may be used, as summarised in Table 5.

Table 5

## SUMMARY OF GASTROPROTECTIVE AGENTS IN RA

Proton pump inhibitors (PPIs) <sup>65</sup>	<i>most effective</i>
Prostaglandin analogues <sup>66</sup>	<i>effective, but less well tolerated compared to PPIs and a problem in premenopausal women</i>
Histamine H <sub>2</sub> receptor antagonists	<i>less effective than PPIs</i>
Mucosal protective agents (e.g. sucralfate)	<i>less effective than PPIs</i>

## 4 PHARMACOLOGICAL MANAGEMENT

It is important to note that the use of an enteric coated, parenteral or rectal NSAID preparation is not protective. The systemic effects of NSAIDs are the predominant cause of damage.

## 4.2.3 RENAL TOXICITY

NSAID use is also associated with renal disease. Prostaglandins regulate and maintain intrarenal perfusion particularly under conditions where renal blood flow may be reduced (e.g. dehydration or blood loss, cardiac failure, chronic renal failure, diuretic use, or hypertension). By inhibiting prostaglandin synthesis under these conditions, NSAIDs may further impair intrarenal blood flow contributing to renal impairment (or overt renal failure), hyperkalaemia, oedema and hypertension. These problems are particularly likely in the elderly.

Interstitial nephritis is an uncommon, idiosyncratic side effect, unrelated to the above pharmacological action of NSAIDs.

No currently available NSAID has a completely safe renal profile. The effects of the new Cox2 agents (see section 4.2.4) on renal profile are as yet unknown. Preliminary work suggests that the effects of Cox2-selective NSAIDs on renal function are similar to those observed with non-selective NSAIDs.<sup>67</sup>

## 4.2.4 NEWER NSAIDS

Recent developments have concentrated on Cox pathways. Cox2-selective NSAIDs target the inhibition of inflammatory pathways while having less effect on cytoprotection and regulatory effects than Cox1. Endoscopic ulceration is no more than for placebo with celecoxib.<sup>68</sup> A recent comparative study of the Cox2-selective NSAID, celecoxib, compared with diclofenac in RA suggested equivalent efficacy with lower frequency of GI ulceration.<sup>69</sup> Similar findings with regard to upper GI tract were noted with celecoxib in comparison with naproxen<sup>70</sup> and ibuprofen and diclofenac.<sup>71</sup> The incidence of upper GI complication with rofecoxib (at present unlicensed for RA) has also been shown to be less than that with naproxen.<sup>72</sup> In this study, both drugs exhibited similar efficacy.

As with all new drugs, the safety of Cox2 inhibitors remains under close review.<sup>73, 74</sup>

## 4.2.5 SUMMARY OF STRATEGIES TO MINIMISE THE RISK OF NSAID TOXICITY

**The lowest NSAID dose compatible with symptom relief should be prescribed.**  
**NSAIDs should be reduced and if possible withdrawn when a good response to DMARDs is achieved.**

- ☒ Simple analgesics should be used in place of NSAIDs if possible and DMARDs should be introduced early to suppress disease activity.
- ☒ Only one NSAID should be prescribed at a time.

**Introduce gastro-protection in RA patients > 65 years and in those with a past history of peptic ulcer.**

- ☒ Consider intra-articular steroids, particularly when disease is localised (see section 4.5).
- ☒ NSAIDs should be avoided in patients taking anticoagulants or corticosteroids.

### 4.3 DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)

DMARDs are drugs which have a beneficial effect on the course of RA, as well as providing symptomatic benefit. Onset of benefit is slow (four to 16 weeks). The currently available agents, associated adverse effects, and their monitoring requirements are indicated in Table 6. Patients should be informed of the potential benefits, risks and monitoring requirements of these drugs.

#### 4.3.1 EVALUATION OF DMARDs

Although the majority of the placebo-controlled studies on DMARDs were carried out in the 1960s, '70s and '80s with methodology which would not necessarily achieve the standards expected in the 1990s, studies have clearly shown benefit from existing DMARDs.<sup>75-82</sup> The Felson meta-analysis<sup>75</sup> of 66 trials in 5,343 patients showed a significant improvement in articular index and ESR.

*Evidence level 1<sup>+</sup>*

Further supportive evidence for the use of DMARDs comes from cohort studies where increased disease modifying anti-rheumatic drug use was strongly correlated with better long-term disability index values.<sup>83</sup>

*Evidence level 1<sup>+</sup>*

There is clear evidence from placebo controlled trials that DMARDs reduce symptoms in RA (as measured by joint pain, swelling, and tenderness, and duration and severity of morning stiffness). DMARDs also improve global wellbeing as assessed by both patient and physician.<sup>81, 83-88</sup>

Inflammatory markers such as ESR, CRP and elevated platelet count are reduced significantly by DMARDs (but not by NSAIDs) and this is associated with better long-term outcome.<sup>21, 81, 83-87</sup> An improvement in anaemia of chronic disease is often observed. There is also consistent evidence that DMARDs have a beneficial effect on functional status, as measured, for example, by HAQ score.<sup>83, 85, 86, 89</sup> Most DMARDs have been shown to have some effect in retarding radiological progression of disease.<sup>85, 90, 91</sup>

#### 4.3.2 COMPARISON OF DMARDs

The best DMARDs for the treatment of RA are those that provide the most efficacy with the least toxicity over the long term.

Data are available from Fries *et al* and the large ARAMIS database, from the Felson meta-analyses and from direct comparative studies.<sup>60, 75, 78, 81, 83, 85, 87, 91-96</sup> The range of well-established DMARDs and a brief summary of the advantages and adverse events associated with each is illustrated in Table 6. Recommendations on the choice of DMARD are made in section 4.3.8.

*Evidence level 1<sup>+</sup>*

#### 4.3.3 TIMING OF DMARD TREATMENT IN RA

It is becoming increasingly clear that DMARDs should be introduced as soon as possible. Four recent studies have highlighted the importance of early intervention with DMARDs.<sup>81, 86-88</sup> Protracted benefit may be achieved in RA patients if appropriate DMARD therapy is introduced early.

*Evidence level 1<sup>+</sup>*

While longer disease duration prior to initiation of DMARDs does not influence the beneficial effect on symptoms or the acute phase response it does have an adverse effect on functional outcome. There is also evidence that delays in initiating DMARDs lead to long lasting negative effects on disease course.<sup>81, 88</sup> There is clear evidence that patients with early disease respond better to treatment.<sup>81</sup>



**Early DMARD therapy in RA is important to maintain function and reduce later disability.**

## 4 PHARMACOLOGICAL MANAGEMENT

## 4.3.4 SUSTAINED DMARD THERAPY

While early initiation of therapy is of importance, a sustained input is vital if disease suppression is to be maintained. Remission (see Annex 3) is the goal but is seldom achieved. Equally 'cure' is not attained, thus withdrawal of treatment is seldom appropriate.

Two randomised placebo controlled studies have demonstrated relapse on withdrawal of disease modifying agents.<sup>97, 98</sup> In both these studies, disease modifying effect was unequivocal. These results confirm the efficacy of DMARDs in comparison with placebo, and demonstrate that sustained prescription of DMARDs is necessary to suppress disease activity. Serial use of DMARDs has been shown to be safe after 10-15 years.<sup>37, 99</sup>

Evidence level 1<sup>+</sup>

**DMARD therapy should be sustained in inflammatory disease in order to maintain disease suppression.**

## 4.3.5 LATE HARM

Uncontrolled disease activity can cause late harm to the patient and this must be weighed against concerns about cumulative or late toxicity when selecting the most appropriate DMARD.<sup>100</sup>

Although evidence relating to late harm is patchy and incomplete, the development of malignancies in patients treated with immunosuppressive drugs has been studied.<sup>101-103</sup> In patients who had developed either neoplasms of the immune system or skin or bladder cancer, the adjusted incidence rate ratio for those in the highest cumulative exposure group was 3.7 compared with those in the lowest exposure group.<sup>103</sup>

## 4.3.6 EFFICACY OF DMARDs

Meta-analysis suggests similar efficacy of sulphasalazine, IM gold, penicillamine and methotrexate.<sup>75</sup> Double-blind RCTs show equal efficacy of sulphasalazine and methotrexate. Drugs of reduced efficacy from open RCTs include hydroxychloroquine and auranofin.<sup>80, 92, 93</sup>

Evidence level 1<sup>+</sup>

Recent studies suggest sulphasalazine,<sup>85</sup> methotrexate<sup>96</sup> and leflunomide have comparable efficacy (details of ACR 20 and ACR 50 are shown in Annex 7). There are no data from adequate studies with respect to azathioprine.

A beneficial effect on radiological progression of RA has been shown with all DMARDs except hydroxychloroquine (which has been shown to have less effect than sulphasalazine in at least one RCT).<sup>93</sup>

- ☒ DMARD choice should take into account patient preference and existing co-morbidity.



**Sulphasalazine, methotrexate, IM gold, and penicillamine are equally effective DMARDs.**

## 4.3.7 TOXICITY OF DMARDs

Toxicity assessment in the initial Felson meta-analysis came from 71 clinical trials that contained 129 treatment groups.<sup>75</sup> Over one year almost one third of the patients (30.3%) stopped therapy. Half of these did so because of drug toxicity. In this meta-analysis injectable gold had higher toxicity rates and higher total dropout rates than the other drugs. Antimalarials and auranofin had relatively low rates of toxicity. In a subsequent meta-analysis the same authors updated their previous meta-analyses by adding trials published through 1990 and trials of azathioprine.<sup>76</sup> Antimalarial drugs



Table 6: DMARD PROFILES

Established DMARDs	Common/minor adverse events	Rare/severe adverse events	Monitoring requirements	Advantages of this drug
Hydroxychloroquine <sup>78, 80, 104, 105, 116, 118</sup>	Nausea, headaches	Retinal toxicity	Eye check* Reduce dose if renal impairment	No blood monitoring required Can use when uncertain of diagnosis (e.g. inflammatory arthritis, connective tissue disease) Can use despite leucopenia or thrombocytopenia
Sulphasalazine <sup>85, 92, 106-108</sup>	Nausea, diarrhoea, headache Mouth ulcers, rash, Oligospermia (reversible) Staining of soft contact lenses Abnormal LFTs	Leucopenia	FBC Liver and renal function Urinalysis	Rapid onset action (8-12 weeks) Can use when uncertain of diagnosis (e.g. reactive/ psoriatic/ RA) Relatively safe in thrombocytopenia
Methotrexate <sup>**94, 96, 109, 110, 111, 114</sup>	Nausea, diarrhoea Mouth ulcers, rash Alopecia Abnormal LFTs	Leucopenia/ Thrombocytopenia Pneumonitis Sepsis Liver disease (late) Nodulosis Epstein-Barr virus associated-lymphoma	FBC Liver and renal function Advise to restrict alcohol intake	Rapid onset action (6–10 weeks) Can use when uncertain of diagnosis (e.g. RA, psoriatic/ connective tissue disease) Can be given orally, IM or SC Weekly administration
IM gold <sup>80, 81, 94</sup>	Mouth ulcers, rash Nitritoid reactions***	Thrombocytopenia/ Leucopenia Proteinuria Colitis	FBC Liver and renal function Urinalysis	Patient preference Ensures compliance
Penicillamine <sup>80, 112</sup>	Nausea/loss of taste Dose related, reversible fall in platelet count	Proteinuria Late autoimmune disease	FBC U&E Urinalysis	
Auranofin <sup>84, 92</sup>	Diarrhoea	Leucopenia	FBC Renal function Urinalysis	Oral gold option
Azathioprine <sup>113</sup>	Nausea	Leucopenia Sepsis Lymphoma (late) <sup>103</sup>	FBC Liver function	Can use in patients with renal disease
Leflunomide <sup>83, 96, 114</sup>	Alopecia Diarrhoea Nausea Rash	Leucopenia Hepatitis Thrombocytopenia	FBC Liver and renal function BP monitoring	Remain to be established (recently introduced)
Cyclosporin <sup>115</sup>	Paraesthesia/tremor/ headaches Hypertrichosis Gingival hypertrophy Nausea	Hypertension Renal disease Sepsis	Liver and renal function BP monitoring	
<p>* see ophthalmology<sup>116</sup> and BSR guidelines<sup>117</sup> (see Annex 11 for website addresses) and relevant datasheets<sup>118</sup></p> <p>** supplement with folic acid<sup>123</sup></p> <p>*** vasomotor symptoms post-injection – a feature seen early in treatment which usually resolves if treatment is continued</p>				
<b>Other DMARDs</b>				
Minocycline <sup>119-122</sup>	Although three recent RCTs have shown an effect of minocycline compared with placebo at present it is not licensed for treatment of RA. Dizziness and skin pigmentation are common side effects.			

## 4 PHARMACOLOGICAL MANAGEMENT

had the lowest toxicity rate of all those studied, but efficacy was only moderate. Methotrexate had the most favourable efficacy/toxicity trade off. Sulphasalazine scored close to methotrexate but in that meta-analysis was slightly more toxic.

A meta-analysis of RCTs of folic or folinic acid supplementation during low dose methotrexate therapy for RA showed that 5 mg folic acid weekly is useful in reducing mucosal and gastrointestinal side effects.<sup>110, 123</sup>

## 4.3.8 CHOICE OF DMARD

Overall there is consistent evidence that hydroxychloroquine and auranofin<sup>75, 76, 92, 93</sup> are relatively weak DMARDs with a slower onset of action, while intramuscular gold, penicillamine, sulphasalazine<sup>92</sup> and methotrexate<sup>75, 76</sup> have very comparable clinical effects on disease activity. More patients are likely to continue on sulphasalazine (and with better effect) compared to auranofin and on methotrexate compared with other DMARDs.



**Sulphasalazine and methotrexate are the current DMARDs of choice due to their more favourable efficacy/toxicity profiles.**

Successive DMARDs are required for most patients in the medium to long term.<sup>124</sup>

## 4.3.9 PRACTICAL PRESCRIBING OF DMARDs

- ☑ Patients should be counselled about the benefits and risks of specific DMARDs, and should be provided with additional written information.
- ☑ Good liaison between primary and secondary care is essential. Rheumatology nurse specialists have an important role in this aspect of care.
- ☑ Monitor for continued efficacy (ESR/CRP, number of tender and swollen joints, duration of morning stiffness, function).
- ☑ Monitor toxicity using British Society of Rheumatology/local guidelines or manufacturers' data sheet recommendations.
- ☑ Clear advice about the monitoring of specific DMARDs should be available to the patient, GP and practice nurse.

## 4.3.10 COMBINATION DMARD THERAPY

Combination DMARD therapy in RA is being increasingly used by rheumatologists, but evidence of benefit remains patchy.

A meta-analysis in 1994 concluded that combination therapy does not offer a substantial improvement in efficacy,<sup>125</sup> whilst toxicity was increased.

*Evidence level 1<sup>+</sup>*

Since the 1994 Felson meta-analysis<sup>125</sup> there have been six parallel (five blind,<sup>126-130</sup> one open<sup>131</sup>), five step-up<sup>132-136</sup> (two using biological agents<sup>128, 135</sup>) and one step-down, combination DMARD<sup>137</sup> studies. Overall the results have been disappointing.

The addition of cyclosporin to methotrexate in patients with established RA has been shown to be of benefit, but it is not known if the same effect could have been achieved by changing to cyclosporin alone.<sup>133</sup> Benefit of a combination of methotrexate, sulphasalazine and hydroxychloroquine has been shown but was not studied in early disease.<sup>128</sup> A recent controlled study of iv infliximab in patients with partial response to methotrexate provided additional clinical benefit and prevented further radiological damage. However, the study was conducted in patients with longer disease duration than applies to the patients covered by this guideline.<sup>136</sup>

*Evidence level 1<sup>+</sup>*

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One study used very high doses of prednisolone (60 mg daily initially) which could not be sustained for prolonged periods in clinical practice without unacceptable cumulative toxicity.<sup>137</sup>

A recent open combination study using a variety of DMARDs showed significantly more patients in remission in the combination group and adverse events were of similar frequency. However, the mean improvement in symptoms, clinical signs and function were similar across the groups making this analysis difficult to interpret.<sup>131</sup>

*Evidence level 1<sup>+</sup>*

In the treatment of poor prognosis early RA, the combination of methotrexate, cyclosporin and targeted intra-articular steroid did not have significant advantages over monotherapy with sulphasalazine in terms of joint damage and function after one year.<sup>138</sup>

Benefit was seen with the addition of etanercept to methotrexate in RA patients with long disease duration and infliximab to methotrexate but at present there is no confirmatory evidence in patients with early disease.<sup>134, 135</sup>



**At present the balance of evidence does not support the routine use of combination DMARD therapy in early RA.**

#### 4.4 TARGETED IMMUNOTHERAPY

Tumour necrosis factor (TNF) is a product of macrophages which acts on the immune system to induce the production of powerful pro-inflammatory mediators. TNF is thus a potential molecular target for the treatment of RA. Two agents with anti-TNF activity have recently become available for RA patients:

1. Infliximab – a chimeric monoclonal antibody which is given as an intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks. Side effects include mild infusion reactions and development of antibodies. Infliximab has been used with methotrexate in part to suppress antibodies against the drug. Results from a double-blind study as an addition to methotrexate have shown encompassing ACR 20 and 50 responses. There was also one death during the period of the study.<sup>134</sup>
2. Etanercept is a TNF receptor fusion protein designed to bind circulatory TNF. It can be administered alone or with methotrexate. It is given as twice weekly subcutaneous injection. Results from placebo-controlled studies are shown in Annex 7. Although no major complications were seen in clinical trials, serious and fatal infections have occurred post-marketing in the USA. A recent double-blind study comparing two doses of etanercept with methotrexate has shown significant advantage of 25 mg etanercept twice weekly in terms of ACR 20, 50 and 70 outcomes and erosion scores. There were also fewer infections in the patients taking etanercept.<sup>139</sup>

There are concerns that continued inhibition of pro-inflammatory molecules may increase the risk of infection and cancer, particularly lympho-proliferative malignancies. Evidence in this respect is still awaited. The exact role of TNF blockade in early disease has yet to be elucidated and their greater costs may preclude widespread early use.

#### 4.5 INTRA-ARTICULAR CORTICOSTEROIDS

Intra-articular corticosteroid injections are widely used to provide rapid, and sometimes sustained, symptomatic relief in 'target' joints.

Intra-articular corticosteroid injections:

- allow local treatment of inflamed joints whilst minimising undesirable systemic effects

- provide symptomatic relief pending the onset of DMARD effect
- treat particularly troublesome joints where the overall disease control is good
- deal with mono/oligo arthritis in instances when DMARDs are deemed inappropriate.

However, there are few controlled trials in this area and no evidence on the long-term effect on disability or radiological progression. Experience from large cohorts suggests that complications such as joint sepsis are very rare.<sup>140</sup> Synovial fluid aspiration at time of joint injection has been shown to reduce relapse rate.<sup>141</sup>

Post-injection rest (24 hours) has shown enhanced improvement in symptomatic relief. Walking times were also improved by this approach.<sup>142</sup>

#### 4.5.1 PRACTICAL PRESCRIBING OF INTRA-ARTICULAR CORTICOSTEROIDS

- ☑ Intra-articular injections can be used for rapid, and sometimes sustained, symptomatic relief in 'target' joints.
- ☑ Intra-articular injections to any one joint should not be given more than three times in one year.
- ☑ When administering intra-articular injections:
  - use sterile technique
  - advise patients how to seek help if joint fails to settle after injection
  - always consider possible septic arthritis in differential diagnosis of mono/oligo flare in RA.

### 4.6 SYSTEMIC CORTICOSTEROIDS – ORAL AND PARENTERAL

#### 4.6.1 SYMPTOMATIC BENEFIT

The symptom relieving anti-inflammatory effects of corticosteroids are well established.<sup>143</sup> Recent randomised controlled studies have shown that this benefit is not sustained beyond nine months when either continuous low-dose corticosteroids (7.5 mg/day)<sup>144</sup> or high-dose 'step-down' therapy,<sup>137</sup> is given as an adjunct to DMARDs or NSAIDs.

*Evidence level 2<sup>+</sup>*

Bridge corticosteroids (usually IM) are an option to provide symptomatic relief until DMARDs become effective. These show benefit in some patients but their value is limited by possible 'rebound' flare of symptoms on discontinuation.<sup>143</sup>

#### 4.6.2 ACUTE PHASE RESPONSE

In many trials the effect of corticosteroids has been obscured by the concurrent use of other treatments known to affect the acute phase response. No additional benefit of corticosteroid compared to placebo was seen with low-dose steroid study,<sup>144</sup> but a significantly more rapid fall in the ESR was apparent with the higher doses used by Boers.<sup>137</sup> The effect on acute phase response had disappeared by one year (by which time the corticosteroid had been discontinued).

#### 4.6.3 FUNCTIONAL RESPONSE

Although some benefit in function from corticosteroids was reported,<sup>145</sup> no objective long term benefit was discerned. Recent studies using the well-validated health assessment questionnaire (HAQ)<sup>17</sup> to measure function have

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shown an early advantage of high-dose 'step-down' corticosteroids.<sup>137</sup> However, the improved HAQ scores seen with adjunctive continuous low-dose steroid were no longer significant by one year and disappeared beyond 15 months.<sup>144</sup> To date, no controlled study of systemic corticosteroid has truly addressed the important assessment of disability as a long term outcome.

## 4.6.4 RADIOLOGICAL PROGRESSION

A number of early studies suggested that oral corticosteroids may inhibit radiological damage and recent randomised controlled trials confirm this finding.<sup>137, 144</sup>

The development of new erosions was reduced by 23% and the progression of existing damage was highly significantly retarded on hand x-rays of patients taking low-dose corticosteroid for two years.<sup>144</sup> On discontinuing corticosteroid therapy radiological progression was again seen at pre-treatment rate.<sup>146</sup>

*Evidence level 1<sup>+</sup>*

A high dose step-down regimen of corticosteroid with combination DMARD also demonstrated inhibition of erosions but had no effect on joint narrowing.<sup>137</sup>

It should be noted that a significant proportion of placebo treated patients in both studies did not develop erosions during the study.<sup>137, 144</sup>

## 4.6.5 CUMULATIVE TOXICITY

Osteoporosis was not formally measured in the Kirwan trial of continuous low-dose oral corticosteroid.<sup>144</sup> In a cohort study of 8,068 patients given a mean dose of 5 mg of prednisolone per day, both reduced bone mineral density and increased fractures were demonstrated over four years. A relative fracture risk of 2:1 was derived for corticosteroid use after correction for multiple variables.<sup>148</sup>

*Evidence level 2<sup>+</sup>*

Two case control studies show increased adverse events in corticosteroid treated rheumatoid arthritis patients, including cataracts, infections (the Committee on Safety of Medicines has drawn attention to the risks of chicken pox exposure in patients not previously infected<sup>148</sup>), gastrointestinal bleeds, avascular necrosis and fractures.<sup>149-151</sup> Increased mortality has also been reported.<sup>152</sup> There is the possibility that corticosteroid treated patients may have had more severe disease.


Both cumulative and average steroid doses are independent, important adverse event predictors.<sup>151</sup> Longer term studies are required to identify the cumulative long-term effect from continuous low-dose corticosteroid and from step-down or intermittent regimens.

Most clinicians withdraw oral corticosteroids slowly (e.g. 1 mg/month when below 15 mg daily) to avoid rebound flare of symptoms.


## 4.6.6 PRACTICAL PRESCRIBING OF SYSTEMIC CORTICOSTEROIDS


The short term symptomatic benefit of systemic corticosteroids and the apparent prevention of radiological damage must be weighed against the risk of significant morbidity. Until additional, adequately powered and long term studies are performed to address the benefits and risks the routine use of oral corticosteroids cannot be recommended. In specific situations where there are strong contraindications to NSAID prescription, or difficulties in using DMARDs, systemic corticosteroids may be acceptable.

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 **Oral corticosteroids are not recommended for routine use, as there is no sustained clinical or functional benefit and there is high risk of toxicity with long term use.**

- ☒ Inform patients of the risks of corticosteroids prior to prescription and issue a steroid warning card.
- ☒ Intramuscular corticosteroid allows control of dose and duration of therapy and may be preferable to oral therapy.
- ☒ Oral corticosteroids should be withdrawn slowly to avoid rebound flare of symptoms.

 **The lowest possible dose of corticosteroid should be used for the shortest possible time.**

 **Monitor patients closely for adverse corticosteroid effects. Be alert to the possibility of diabetes, cataract and infection. Inform patients not previously infected of the danger of chicken pox/shingles exposure.**

- ☒ Ensure adequate prophylaxis and treatment of osteoporosis in patients taking oral corticosteroids.

#### 4.7 COMPLEMENTARY MEDICINE

Few studies in this field relate specifically to rheumatoid arthritis and many studies have been excluded from the guideline on the grounds of small numbers and poor design.

There is unsatisfactory evidence of possible subjective benefit of homeopathy over placebo.<sup>153–155</sup> A proprietary remedy 'Rheumalex' appeared to help in pain relief, but the herbal substance feverfew showed no evidence of benefit.<sup>156, 157</sup> Acupuncture showed no benefit in one meta-analysis reviewed but the quality of this analysis was limited.<sup>158, 159</sup> There is no evidence that Seatone or selenium produced any clinical benefit.<sup>160–162</sup>

While no evidence of effectiveness is not the same as evidence of ineffectiveness the lack of adequate research studies precludes firm conclusions. Patients have a perception that because these treatments are 'natural' they are without side effects but this is not the case.<sup>163</sup>

Further research is clearly needed and should include close monitoring of possible harm as well as potential benefit.

#### 4.8 OTHER THERAPIES

##### 4.8.1 HORMONE REPLACEMENT THERAPY

Although RA patients on hormone replacement therapy (HRT) have been shown to report a significant increase in general wellbeing compared with placebo, there is to date no evidence of alteration in indices of disease activity.<sup>164, 165</sup> HRT is of undoubted benefit in improving bone mineral density in postmenopausal women with RA and associated osteoporosis.<sup>166</sup>

##### 4.8.2 IRON THERAPY

Anaemia is common in RA and is not always due to iron deficiency. Unnecessary iron supplements should be avoided. Patients who are truly iron deficient should be assessed and any dietary deficiency should be corrected. GI blood loss requires investigation and specific therapy e.g. proton pump inhibitor (see section 4.2.2). Ferritin acts as an acute phase reactant in RA, thus a 'normal' ferritin does not exclude iron deficiency.

## 5 The role of the multidisciplinary team

- ☑ The multidisciplinary team has been shown to be effective in optimising management of patients with RA.<sup>38</sup> All patients should have access to a range of health professionals, including general practitioner, rheumatologist, nurse specialist, physiotherapist, occupational therapist, dietitian, podiatrist, pharmacist and social worker.

### 5.1 OCCUPATIONAL THERAPY

In everyday practice, the substantial impact of skilled occupational therapy (OT) intervention on quality of life for patients with RA is clear. Unfortunately, relatively few studies have been carried out and evidence from RCTs is often lacking. The OT approach is multifaceted and includes:

#### 5.1.1 ACTIVITIES OF DAILY LIVING

Facilitation of the activities of daily living (e.g. washing, toileting, dressing, cooking, eating, working), sometimes with the provision of equipment and adaptations, is fundamental to the management of RA.<sup>167</sup> Effective OT advice is crucial in helping patients to maximise function and improve their level of independence.

*Evidence level 1<sup>+</sup>*



**Skilled occupational therapy advice should be available to those experiencing limitations in function.**

#### 5.1.2 JOINT PROTECTION

Joint protection aims to reduce pain and stress on joints whilst carrying out everyday activities.<sup>168</sup>

*Evidence level 4*

A range of strategies are employed including adapting movement patterns of affected joints to reduce strain, assistive devices, rest regimens, energy conservation techniques, exercise and splinting. These interventions are difficult to evaluate and formal studies are limited. Studies in patients with longer disease duration, have shown encouraging results.

### 5.2 PHYSIOTHERAPY

The role of the physiotherapist in assessing and treating patients with RA is well recognised in clinical practice. Physiotherapy management has been shown to be effective in improving self-efficacy, knowledge and morning stiffness.<sup>169</sup> However, well-conducted studies evaluating the effectiveness of intervention are lacking and the formal evidence base is limited.

#### 5.2.1 DYNAMIC EXERCISE THERAPY

Exercise therapy is prescribed in an attempt to overcome the adverse effects of RA on muscle strength, endurance and aerobic capacity. Dynamic exercise therapy (i.e. exercises of low to moderate aerobic intensity) is effective in increasing aerobic capacity and muscle strength. No adverse effects on disease activity or pain are observed.<sup>170</sup> Limited evidence indicates that specific strength training programmes can reduce impairment.<sup>171</sup>

*Evidence level 1<sup>++</sup>*



**Patients should be encouraged to undertake simple dynamic exercises.**